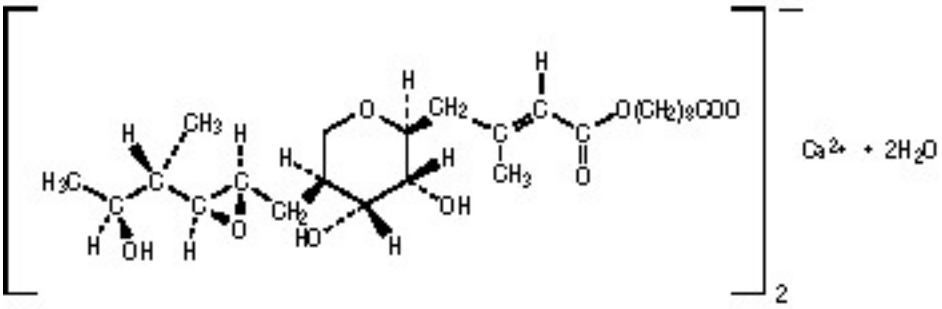
BACTROBAN - mupirocin calcium ointment
SmithKline Beecham Corporation

DESCRIPTION

BACTROBAN NASAL (mupirocin calcium ointment, 2%) contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6. The structural formula of mupirocin calcium is:



BACTROBAN NASAL is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% pure mupirocin free acid) in a soft white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (SOFTISAN® 649).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following single or repeated intranasal applications of 0.2 gram of BACTROBAN NASAL 3 times daily for 3 days to 5 healthy adult male subjects, no evidence of systemic absorption of mupirocin was demonstrated. The dosage regimen used in this study was for pharmacokinetic characterization only. (See DOSAGE AND ADMINISTRATION for proper clinical dosing information.)

In this study, the concentrations of mupirocin in urine and of monic acid in urine and serum were below the limit of determination of the assay for up to 72 hours after the applications. The lowest levels of determination of the assay used were 50 ng/mL of mupirocin in urine, 75 ng/mL of monic acid in urine, and 10 ng/mL of monic acid in serum. Based on the detectable limit of the urine assay for monic acid, one can extrapolate that a mean of 3.3% (range: 1.2 to 5.1%) of the applied dose could be systemically absorbed from the nasal mucosa of **adults**.

Data from a report of a pharmacokinetic study in neonates and premature infants indicate that, unlike in adults, significant systemic absorption occurred following intranasal administration of BACTROBAN NASAL in this population. **At this time, the pharmacokinetic properties of mupirocin following intranasal application of BACTROBAN NASAL have not been adequately characterized in neonates or other children less than 12 years of age, and in addition, the safety of the product in children less than 12 years of age has not been established.**

The effect of the concurrent application of intranasal mupirocin calcium ointment, 2% with other intranasal products has not been studied. (See PRECAUTIONS, Drug Interactions.)

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, demonstrates no antibacterial activity. In a study conducted in 7 healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. Monic acid is predominantly eliminated by renal excretion. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this mode of action, mupirocin demonstrates no in vitro cross-resistance with other classes of antimicrobial agents.

When mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1,024 mcg/mL) has been reported in some strains of *Staphylococcus aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved topically by intranasal administration. However, the minimum bactericidal concentration (MBC) against relevant intranasal pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of nasal secretions on the MICs of intranasally applied mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of methicillin-resistant *S. aureus*, both in vitro and in clinical studies of the eradication of nasal colonization. BACTROBAN NASAL only has established clinical utility in nasal eradication as part of a comprehensive program to curtail institutional outbreaks of infections with methicillin-resistant *S. aureus*. (See INDICATIONS AND USAGE.)

The following in vitro data are available, **but their clinical significance is unknown**. Mupirocin exhibits in vitro MICs of 1 mcg/mL or less against most (>90%) strains of methicillin-susceptible *S. aureus*; however, the safety and effectiveness of mupirocin calcium in eradicating nasal colonization of and preventing subsequent infections due to methicillin-susceptible *S. aureus* have not been established.

INDICATIONS AND USAGE

BACTROBAN NASAL is indicated for the eradication of nasal colonization with methicillin-resistant *S. aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S. aureus* infection during institutional outbreaks of infections with this pathogen.

NOTE:

1. There are insufficient data at this time to establish that this product is safe and effective as part of an intervention program to prevent autoinfection of high-risk patients from their own nasal colonization with *S. aureus*.

2. There are insufficient data at this time to recommend use of BACTROBAN NASAL for general prophylaxis of any infection in any patient population.

3. Greater than 90% of subjects/patients in clinical trials had eradication of nasal colonization 2 to 4 days after therapy was completed. Approximately 30% recolonization was reported in 1 domestic study within 4 weeks after completion of therapy. These eradication rates were clinically and statistically superior to those reported in subjects/patients in the vehicle-treated arms of the adequate and well-controlled studies. Those treated with vehicle had eradication rates of 5% to 30% at 2 to 4 days post-therapy with 85% to 100% recolonization within 4 weeks.

All adequate and well-controlled trials of this product were vehicle-controlled; therefore, no data from direct, head-to-head comparisons with other products are available at this time.

CONTRAINDICATIONS

BACTROBAN NASAL is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

AVOID CONTACT WITH THE EYES. Application of BACTROBAN NASAL to the eye under testing conditions has caused severe symptoms such as burning and tearing. These symptoms resolved within days to weeks after discontinuation of the ointment. In the event of a sensitization or severe local irritation from BACTROBAN NASAL, usage should be discontinued.

PRECAUTIONS

General

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi. (See DOSAGE AND ADMINISTRATION.)

Information for Patients

Patients should be given the following instructions:

- Apply approximately one-half of the ointment from the single-use tube directly into 1 nostril and the other half into the other nostril;
- Avoid contact of the medication with the eyes;
- Discard the tube after using, do not re-use;
- Press the sides of the nose together and gently massage after application to spread the ointment throughout the inside of the nostrils; and
- Discontinue usage of the medication and call your healthcare practitioner if sensitization or severe local irritation occurs.

Drug Interactions

The effect of the concurrent application of intranasal mupirocin calcium and other intranasal products has not been studied. Until further information is known, mupirocin calcium ointment, 2% should not be applied concurrently with any other intranasal products.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.
Reproduction studies were performed in rats with mupirocin administered subcutaneously at doses up to **40** times the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy

Teratogenic Effects: Pregnancy Category B
Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 65 and 130 times, respectively, the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BACTROBAN NASAL is administered to a nursing woman.

Pediatric Use
Safety in children under the age of 12 years has not been established. (See CLINICAL PHARMACOLOGY.)

ADVERSE REACTIONS

Clinical Trials
In clinical trials, 210 domestic and 2,130 foreign adult subjects/patients received BACTROBAN NASAL ointment. Less than 1% of domestic or foreign subjects and patients in clinical trials were withdrawn due to adverse events.
The most frequently reported adverse events in foreign clinical trials were as follows: Rhinitis (1.0%), taste perversion (0.8%), pharyngitis (0.5%).
In domestic clinical trials, 17% (36/210) of adults treated with BACTROBAN NASAL ointment reported adverse events thought to be at least possibly drug-related. The incidence of adverse events that were reported in at least 1% of adults enrolled in domestic clinical trials were as follows:
ADVERSE EVENTS (≥1% INCIDENCE)-ADULTS IN US TRIALS

	% of Subjects/Patients Experiencing Event BACTROBAN NASAL (n=210)
Headache	9%
Rhinitis	6%
Respiratory disorder, including upper respiratory tract congestion	5%
Pharyngitis	4%
Taste perversion	3%
Burning/stinging	2%
Cough	2%
Pruritus	1%

The following events thought possibly drug-related were reported in less than 1% of adults enrolled in domestic clinical trials: Blepharitis, diarrhea, dry mouth, ear pain, epistaxis, nausea, and rash.
All adequate and well-controlled clinical trials have been performed using BACTROBAN NASAL ointment, 2% in 1 arm and the vehicle ointment in the other arm of the study. No adequate and well-controlled safety data are available from direct, head-to-head comparative studies of this product and other products for this indication.

OVERDOSAGE
Following single or repeated intranasal applications of BACTROBAN NASAL to adults, no evidence for systemic absorption of mupirocin was obtained. Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well

tolerated in healthy adult subjects. There is no information regarding local overdose of BACTROBAN NASAL or regarding oral ingestion of the nasal ointment formulation.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE.)

Adults (12 years of age and older): Approximately one-half of the ointment from the single-use tube should be applied into 1 nostril and the other half into the other nostril twice daily (morning and evening) for 5 days.

After application, the nostrils should be closed by pressing together and releasing the sides of the nose repetitively for approximately 1 minute. This will spread the ointment throughout the nares.

The single-use 1.0 gram tube will deliver a total of approximately 0.5 grams of the ointment (approximately 0.25 grams/nostril).

The tube should be discarded after usage; it should not be re-used.

The safety and effectiveness of applications of this medication for greater than 5 days have not been established. There are no human clinical or pre-clinical animal data to support the use of this product in a chronic manner or in manners other than those described in this package insert.

Until further information is known, BACTROBAN NASAL should not be applied concurrently with any other intranasal products.

HOW SUPPLIED

BACTROBAN NASAL is supplied in 1.0-gram tubes.

NDC 0029-1526-11 (package of 10 single-tube cartons).

Store between 20° and 25°C (68° and 77°F); excursions permitted to 15°-30°C (59°-86°F). Do not refrigerate.

REFERENCE

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard. CLSI Document M7-A7. CLSI, Wayne, PA, January 2006.

GlaxoSmithKline
Research Triangle Park, NC 27709

April 2009 BBN:2PI

Principal Display Panel

NDC 0029-1526-03

BACTROBAN NASAL®

MUPIROCIN CALCIUM OINTMENT 2%

1 x 1.0 gram Single-Use Tube

R_x only

Store at 20° - 25°C (68° – 77°F); excursions permitted 15° - 30°C (59° – 86°F).. Do not refrigerate. Each gram contains 21.5 mg mupirocin calcium in a soft white ointment base.

Usual Dosage: For intranasal use only. Apply one-half the contents of a tube in one nostril. Apply other half of tube contents in other nostril. See accompanying prescribing information.

GlaxoSmithKline
Research Triangle Park, NC 27709
Made in England

TO OPEN

1. Turn cap counter-clockwise to puncture the seal.
2. Lift off plastic tip cover.

HOW TO APPLY

Apply one-half the contents of the tube in one nostril. Apply the other half of tube contents in the other nostril.

Press nostrils together. Massage for approximately one minute. Discard tube. Do not reuse.

Avoid contact with eyes. Contact your healthcare professional if you have any questions.

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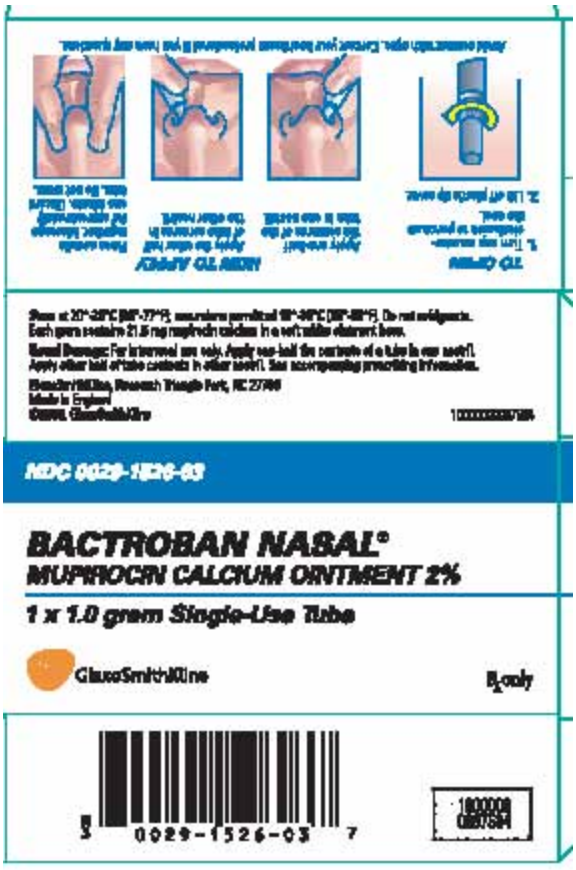

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BACTROBAN NASAL®

MUPIROCIN CALCIUM OINTMENT 2%

1 x 1.0 gram Single-Use Tube

GlaxoSmithKline

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